MERCURIAL DIURETICS*

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INORGANIC mercury compounds were employed as diuretics as early as the 16th century and combinations of mercuric chloride (calomel) and digitalis served as treatment for dropsy in the 19th century.[1, 2] Vogl's chance observation that the anti-syphilitic organomercurial Novasurol produced a diuresis stimulated the use of organomercurials in clinical medicine.[3] When this agent proved too toxic for general use, the efficacy of other organic mercury compounds was investigated.[4] At present the organic mercurials in use are mercurated allyl derivatives with modifications of specific side chains affecting toxicity, solubility or diuretic potency.[5]

Early observations suggested that the diuretic stimulus derived from a nonrenal effect.[6, 7] The classical renal transplant experiments of Govaerts[8] and the studies of Bartram, in which the organic mercurials were injected directly into the renal artery, established the primary renal action of the mercurials.[9] It has been demonstrated that the diuresis is not dependent upon changes in filtration rate or renal plasma flow but results from the inhibition of reabsorption of filtered sodium and chloride ions.[10, 11] It is not certain which of these ions is primarily affected. The demonstration that the increment in chloride excretion often exceeds that in sodium, particularly in salt retaining subjects, and that a hypochloremic alkalosis may result from a mercurial diuresis led some investigators to propose that chloride reabsorption was primarily inhibited.[12, 13] However, recent evidence indicates that the sodium ion, rather than chloride, is actively transported.[14] Micropuncture studies have shown that the intratubular potential, allegedly produced by active sodium transport, is diminished by a mercurial.[15] The relative excess in chloride excretion may then be explained by the exchange of the rejected sodium with potassium or hydrogen at a more distal site.[16]

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A variety of techniques have been utilized to delineate the mechanism and renal tubular site of mercurial action. One line of approach has been based upon an analysis of the morphological lesions produced by the administration of organomercurials. While the most marked changes have been noted in the proximal tubule, lesions have also been seen elsewhere.[17] The precise site seems to be determined by the species studied, the dose administered, and the specific mercurial employed. Moreover, the dose necessary to produce tubular lesions far exceeds that necessary to produce a diuresis. Histochemical methods have also been utilized. An inhibition of succinic dehydrogenase activity during a mercurial diuresis was demonstrated by one group,[18] while another found that the administration of BAL (British anti-lewisite) inhibited both diuresis and enzyme block.[19] It was therefore suggested that some relation existed between availability of -SH bonds and a mercurial diuresis. However, other studies have cast doubt upon the primary importance of the sulfhydryl enzymes.[20, 21] It has been shown that p-chloromercuribenzoate, a potent -SH enzyme inhibitor, failed to provoke a diuresis.[21]

The influence of mercurials on discrete tubular functions was also evaluated in an attempt to delineate the tubular site of action of these agents, but the results of these studies are similarly inconclusive. In man, it was demonstrated that a mercurial diuresis produced a marked fall in TmGlucose and TmPAH, suggesting a proximal tubular site of action.[22, 23] However, in the dog, mercurials of comparable diuretic potency failed to alter these parameters of tubular function.[24] Mercurials did not affect hydrogen or ammonium production, implying no change in distal tubular function.[25] However, mercurials did depress potassium secretion, a function which has been assigned to the late distal tubule.[26, 27]

The largest body of work devoted to determining the site of action of organomercurials has been based on clearance methodology. An understanding of the characteristics of tubular fluid during maximum hydration should help localize the site at which an agent inhibits salt and water reabsorption. Solute-free water (CH_2O) is formed by the active extraction of salt at the ascending limb of the loop of Henle and at the early distal tubule, segments virtually impermeable to water, particularly in the absence of anti-diuretic hormone. Free water clearance, therefore, is calculated as the difference between urine flow (V)

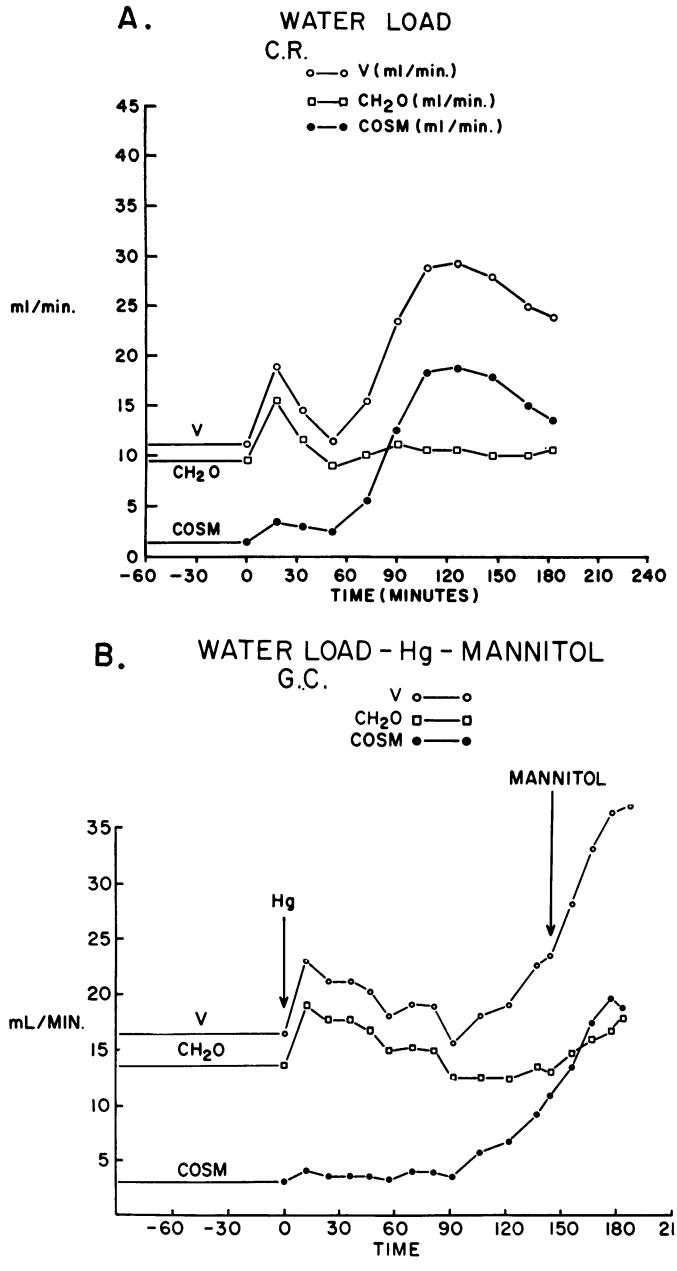

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Fig. 1A. Effect of meralluride on V, CH_2O and Cosm in hydrated subject.

Fig. 1B. Effect of meralluride on V, CH_2O and Cosm in hydrated subject—effect of a superimposed nonspecific solute diuretic.

and solute clearance (Cosm). Experiments have demonstrated that an agent which acts to decrease salt absorption in the proximal tubule, and thus presents more absorbable solute to the early distal tubule, will augment free water clearance.[28, 29] An agent which primarily affects salt absorption at the water clearing site would be expected to depress free water clearance. Previous observations by Wesson and Anslow,[30] Capps and associates[31] and Miller and Riggs[32], employing nontheophylline-containing mercurials, have shown that a mercurial diuresis does not alter the rate of free water clearance. However, it was noted that occasionally a mercurial depressed free water clearance. On the other hand, other observers using theophylline-containing mercurials reported an increase in free water clearance directly after the administration of the mercurial.[28, 33] Experiments performed in our laboratory, in which the characteristics of a mercurial diuresis were studied in maximally hydrated normal man, have helped resolve these differences.[29] A typical experiment, using the theophylline-containing agent meralluride, is shown in Figure 1A. A transient first phase developed promptly, during which a modest increase in solute clearance produced a very conspicuous increment in free water clearance. After the first phase subsided, a much larger increment in solute clearance occurred (accounted for by the increment in salt excretion), without an appreciable change in free water clearance. This increment in solute clearance averaged about 8 per cent of the filtration rate or 9 ml. per minute. Generally, before the major mercurial diuresis developed, free water clearance returned to control levels or to levels below control, but characteristically, the free water clearance remained fixed as the solute diuresis developed. The transient, first phase was duplicated by administering a quantity of aminophylline equivalent to the theophylline contained in the meralluride formula.

When nontheophylline-containing mercurials were employed (Salyrgan and Thiomerin), the characteristic first phase was not evident. The free water clearance tended to fall prior to the development of the major portion of the solute diuresis but, as with meralluride, the quantity of free water generated remained relatively constant as the major portion of the solute diuresis developed. If during the mercurial diuresis a nonspecific proximal diuretic* was administered, free water clearance was enhanced as solute clearance further increased (Figure

* A nonspecific proximal diuretic (mannitol, urea, sulfate, calcium) either actively or passively inhibits proximal tubular absorption of solute and thereby sweeps more isotonic fluid into the distal tubule.

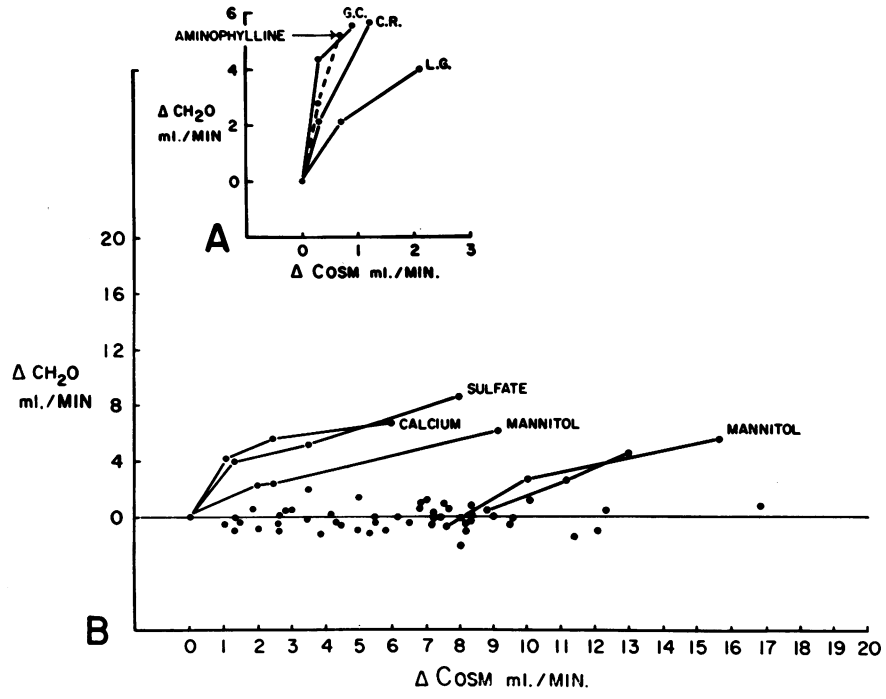

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Fig. 2A. The average change in CH_2O and Cosm produced by aminophylline compared to that noted during the first phase of meralluride diuresis in three subjects.

Fig. 2B. The changes in CH_2O and Cosm produced by a nonspecific solute diuretic compared to those noted during the sustained phase of meralluride diuresis.

1B). This diuresis was qualitatively similar to that produced by the nonspecific diuretics when administered to subjects not undergoing a mercurial diuresis.

The characteristics of the meralluride diuresis in hydrated man are summarized in Figure 2. The upper section (A) of the figure demonstrates the transient first phase of meralluride effect duplicated by aminophylline. The lower section (B) shows that during the development of the mercurial diuresis, free water clearance remained unchanged. It is evident how this type of diuresis differed from that produced by nonspecific proximal agents (shown as the connected lines) where free water clearance continued to rise as solute clearance increased. When the nonspecific agents were superimposed during a

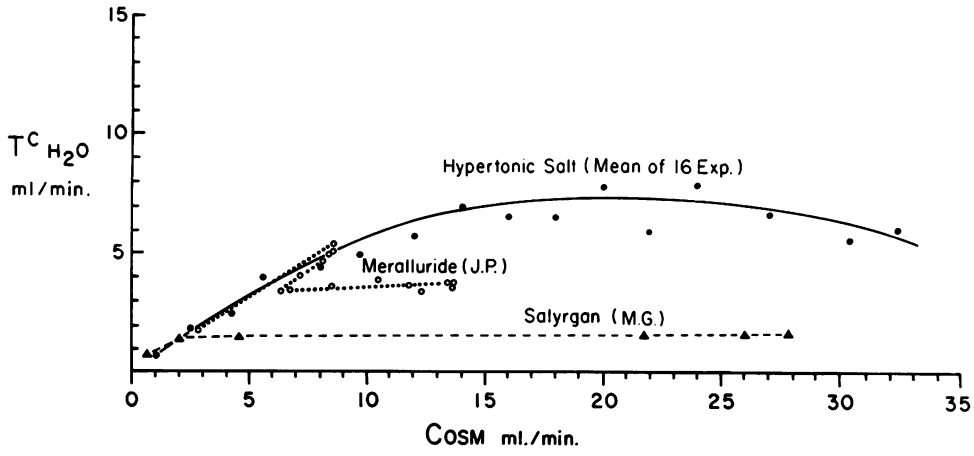

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Fig. 3A. Comparison of the two phases of a meralluride diuresis with the diuresis produced by a nontheophylline-containing mercurial (Salyrgan) and by a nonspecific solute diuretic (hypertonic salt).

mercurial diuresis, it was generally possible to augment free water clearance. These experiments explain why those observers utilizing theophylline-containing mercurials noted a prompt but transient increase in free water clearance. These findings support those observations that recorded no change or a fall in free water clearance after a mercurial diuresis had been established. The significant finding, in our opinion, represents the singular constancy of free water clearance during the development of the salt diuresis. Expressed in other terms, the mercurial diuresis adds to the dilute urine an iso-osmotic rejectate. Nonspecific proximal agents evoke a hypo-osmotic diuresis in that free water clearance is increased. Moreover, when nonspecific agents are superimposed during a mercurial diuresis, a hypo-osmotic rejectate is added to the mercurial-induced iso-osmotic rejectate.

In another series of experiments negative free water clearance (TcH_2O) was measured in maximally hydropenic subjects undergoing mercurial diureses.[34] TcH_2O represents that quantity of water removed from iso-osmotic distal tubular fluid passing through the collecting duct. The quantity of water so extracted determines the final urine tonicity at every level of solute clearance. The magnitude of TcH_2O, to an

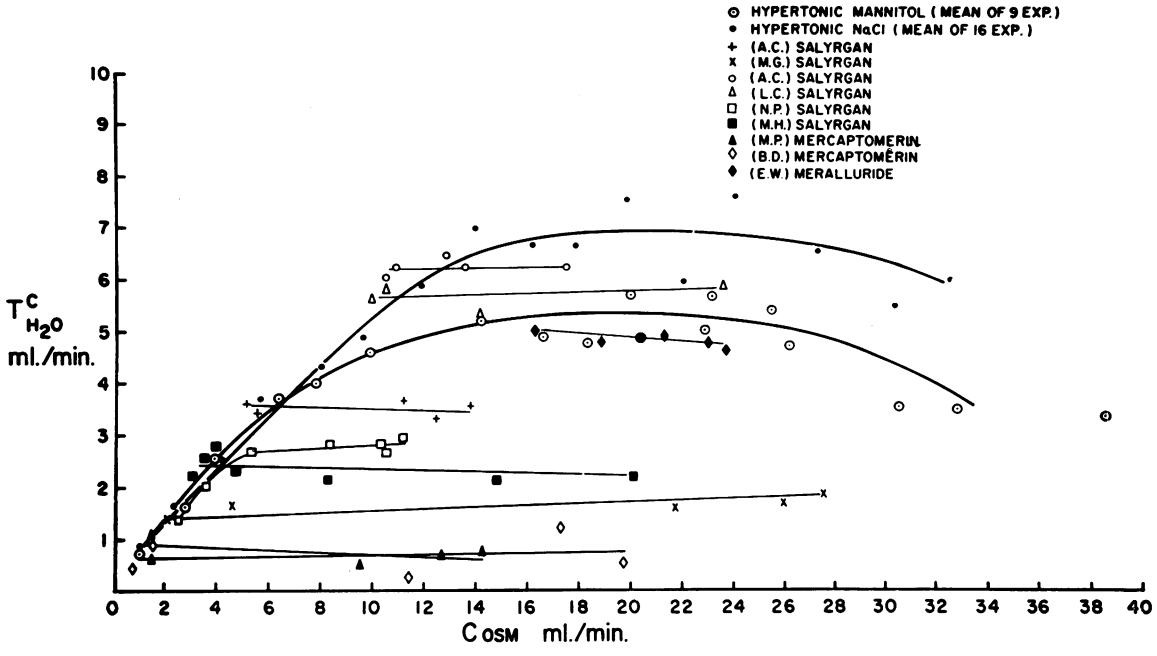

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Fig. 3B. Effect of organomercurials and hypertonic salt and mannitol infusions on solute excretion (Cosm) and free water absorption (TcH_2O).

appreciable extent, depends upon the quantity of sodium extracted by the ascending limb of the loop of Henle and retained within the hypertonic medulla.

The progressive increase in TcH_2O produced by an infusion of hypertonic salt is depicted in Figures 3A-C (upper control curves). The characteristics of two mercurial diureses produced during maximum hydropenia are shown in Figure 3A. In the meralluride experiment, a transient first phase followed the curve produced by the salt infusion. During the more sustained mercurial-induced salt diuresis TcH_2O remained relatively fixed. With the nontheophylline containing mercurial, Salyrgan, the first phase was absent and TcH_2O remained unchanged as salt excretion rose. In Figure 3B the characteristics of the TcH_2O curves produced by nontheophylline containing mercurials are summarized. TcH_2O remained relatively fixed at whatever steady

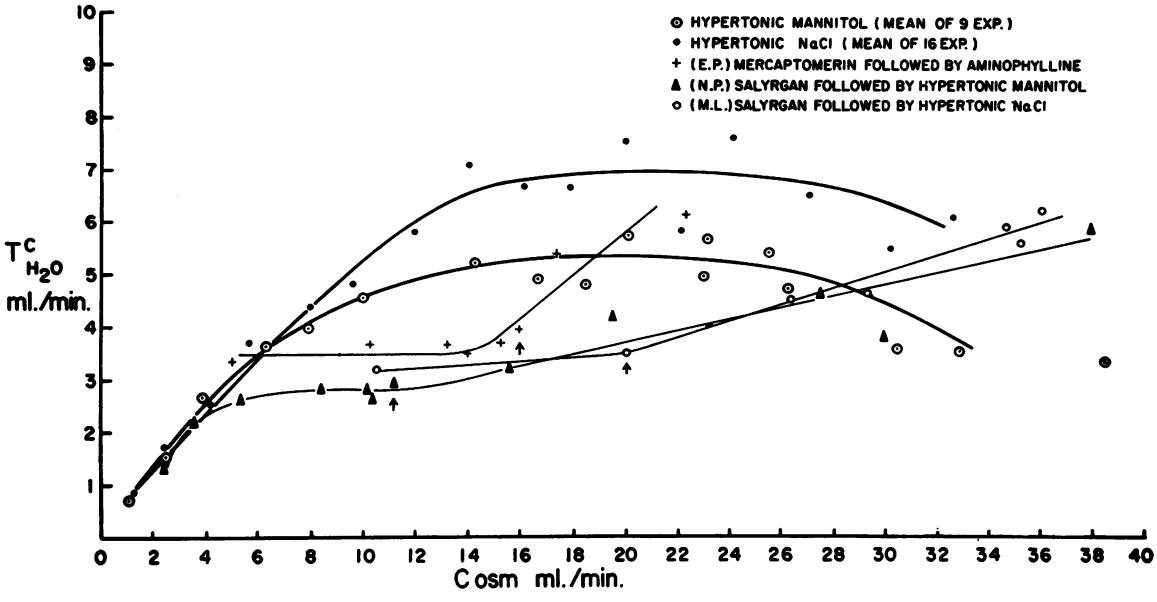

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Fig. 3C. Effect of a nonspecific solute diuretic superimposed on organomercurial diuresis. The arrow indicates the point of administration of the nonspecific agent.

state control level had been established before the mercurial was administered.

If, during the mercurial diuresis, a nonspecific diuretic was administered Tc_{H_2O} generally increased (Figure 3C).

These observations are also evident in the publications of others.[35-37] Specifically, under hydropenic conditions, mercurials produced an increase in salt and water excretion so related that the ratio between these increments defines an iso-osmotic rejectate. One observer, noting the persistently low Tc_{H_2O}, suggested that the mercurial provoked an overt concentrating defect.[37] On the other hand, if Tc_{H_2O} is increased prior to the mercurial diuresis these values persist so that a concentrating defect is not evident.[34] As in the hydrated experiments the qualitatively different transient first phase produced by theophylline contained in meralluride may complicate the analysis.

These data offer some insight into the major tubular locus at which mercurials may act. The characteristics of a mercurial diuresis do not

mimic those of an agent which inhibits proximal salt and water reabsorption. A major sole action within the proximal tubule therefore does not appear consistent with these findings. Similarly, it is difficult to place the locus of action at the ascending limb of the loop of Henle. A major effect at this site without a progressive fall in CH_2O or TcH_2O seems hardly tenable. An hypothesis that would explain these findings demands a balance of proximal and distal tubular effects. One form of such a balance would require that the rate of distal sodium absorption be fixed by the mercurial at whatever level obtained prior to the diuresis so that proximal inhibition would present more iso-osmotic fluid to the distal segment, now converted to an inactive conduit. This hypothesis was tacitly assumed by earlier investigators when they deduced that the distal tubule was virtually saturated under normal conditions.[30] However, micropuncture analyses have clearly demonstrated that with any increase in distal solute supply a variable proportion of the extra load is absorbed.[38] Furthermore, the capacity for free water clearance and TcH_2O to be augmented during a mercurial diuresis tends to exclude this hypothesis. Another balance of proximal and distal effects that could explain these data would demand a unique interrelation, in that the magnitude of the distal block would progressively increase so as to overcome the effect of the increasing solute supply derived from the developing proximal block. At every level of solute clearance net sodium absorption in the ascending limb would thereby remain relatively constant. Although it is not possible to exclude the development of such precisely balanced inhibitory effects, the obvious limitations of this hypothesis have led us to consider another.

This alternative would demand the existence of a late distal tubular site, beyond the water clearing segment, at which salt and water would be extracted in iso-osmotic proportions regardless of the concentration of the parent fluid. An inhibitory effect at such a segment would explain the consistently iso-osmotic nature of the mercurial rejectate without changing sodium supply to the ascending limb, free water clearance or TcH_2O. If more solute were then swept into the ascending limb, CH_2O or TcH_2O would be expected to rise in accordance with our observations. Although the existence of such a late distal segment is difficult to explain in terms of prevailing concepts, a block at such a site would best explain these data.

Stop flow experiments in the dog have suggested that the major

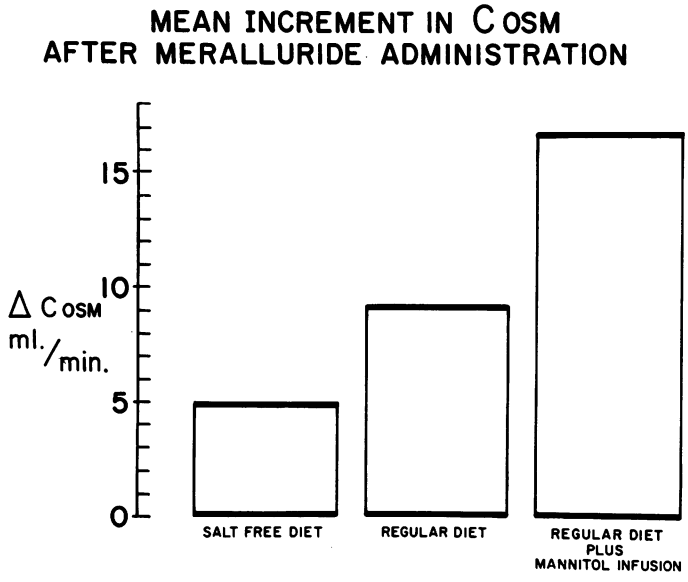

Fig. 4. Comparison of the increase in Cosm after meralluride in the salt-free diet and regular diet and regular diet plus mannitol infusion.

action of the mercurials is confined to the proximal tubule.[39, 40] However, an inhibitory effect in the distal tubule might be obscured by the prolonged interval during which the fluid remains in contact with the nephron in a stop flow experiment. A change in distal tubular function might become evident only when proximal tubular fluid passed the altered distal segment, and spuriously be attributed to the proximal tubule.

The proposal that mercurials may act in the late distal tubule also explains some of the other features of a mercurial diuresis. It has been previously established in dog and man, and also evident in our experiments, that a mercurial diuresis reduces potassium excretion when the control rate of potassium excretion is high.[26, 27, 29] Since the secretion of potassium represents a late distal process probably dependent upon exchange with sodium, an inhibitory influence on active sodium absorption at this site would serve to explain this finding. Alternatively, when potassium secretion is low because of inadequate sodium supply to this and more distal sites, as in the collecting duct, the increased supply of sodium and chloride to the collecting duct will increase potassium

exchange. Under these conditions, the exchange of this increased quantity of sodium for potassium at the collecting duct will overcome the more proximal influence of the mercurial in depressing potassium secretion.

In the course of our studies it became evident that the mean diuresis resulting from a standardized dose of organomercurial could be influenced by salt intake (Figure 4). A salt-free diet reduced the diuresis from a mean Cosm of 9 to 5 ml./min., whereas a prior increase in salt intake or a concomitant mannitol diuresis would augment the diuresis appreciably. These findings could be explained by a distal site of mercurial action. If the mercurial effect were determined by the quantity of salt absorbed by the proposed distal segment, a prior change in the magnitude of the process would alter the mercurial effect proportionately. In the dog, a reduction in filtration rate sharply curtails distal solute supply so that a mercurial diuresis is inhibited.[41] In man, under normal conditions, it may be assumed that approximately 65 to 70 per cent or 80 ml./min. of the filtered load may be absorbed proximally, leaving about 40 ml./min. available for operation by the loop, distal tubule and collecting duct. The absorption of salt from about 20 to 25 ml. of this fluid in the ascending limb would provide adequate solute for the production of medullary hypertonicity and a maximum free water clearance of approximately 14 ml. per minute. Approximately 20 ml. per minute of iso-osmotic fluid, plus a variable quantity of free water, would then remain for operation by the late distal tubule and collecting duct. Blocking the reabsorption of a considerable fraction of this fluid at a distal site could then account for the mean mercurial diuresis of approximately 9 ml. per minute.

The problem of mercurial fastness could be resolved by assuming that a variety of factors, including salt restriction, reduced filtered load, hormonal influences enhancing more proximal salt absorption, all diminish the rate of solute supply to the mercurial sensitive segment. The management of such mercurial fastness must then depend upon the utilization of techniques affecting cardiac and/or renal function so as to augment the supply of salt to this segment.

Proximal agents such as aminophylline, cortisone, mannitol, calcium, are generally nonproductive in the sicker salt-retaining subjects because of the substantial salt-absorptive capacity of the distal tubule. However, when these agents are used simultaneously with others which exert an

TABLE I.—EFFECT OF VARIOUS EXPERIMENTAL AND CLINICAL TECHNIQUES ON MERCURIAL DIURESIS

Augmented	*Unchanged*	*Diminished*
1. Increased GFR[42]	1. Respiratory Acidosis[47]	1. Reduced GFR[41]
2. Increased Salt Intake[12, 43]	2. Respiratory Acidosis and Bicarbonate Infusion[12]	2. Decreased Salt Intake[42, 43]
3. Proximal Diuretics[30, 43, 44]	3. Potassium Deficiency Alkalosis[48]	3. Respiratory Alkalosis[49]
4. Nitrate[12, 45]		4. Bicarbonate Infusion[12, 45, 48]
5. Sulfate[12]		5. Acetazolamide[50, 52]
6. Ammonium Chloride[46, 47]		

inhibitory influence at more distal sites, substantial salureses can be induced even in the most avid salt retainer.

A summary of techniques which have been shown to alter the effectiveness of mercurial diuretics is presented in Table I. Apart from the nonspecific methods, such as increasing the filtered load or salt intake, the majority of these techniques depend upon the administration of acidifying salts. The potentiation of the diuresis by these regimens has been largely attributed to the acidifying nature of these agents.[12] However, it has been recognized that neither the plasma chloride nor the degree of extracellular acidosis represents the responsible factor.[45, 48] Some investigators have observed that, after the administration of ammonium chloride, the extent of chloruresis rather than the degree of acidification correlates with augmentation of the mercurial diuresis.[53] What has been generally overlooked in the use of these acidifying salts is that each provides a relatively impermeant anion which would tend to enhance distal tubular sodium supply. This increased supply might therefore account for a large fraction of the augmenting influence produced by the acidifying as well as the nonspecific measures. Indeed, when a comparable degree of acidosis is produced by the inhalation of CO_2 without provoking an appreciable anion diuresis, the mercurial effect is not augmented.[47] Alternatively, there seems to be little doubt that the presence of alkaline bicarbonate-containing urine, however achieved, does decrease the effectiveness of a mercurial diure-

sis. [12, 45, 48] A bicarbonate infusion or acetazalamide administration, each of which produces bicarbonate-rich urines, act to inhibit a mercurial diuresis, although their effects on extracellular and intracellular pH may be qualitatively different.[50-52] A bicarbonate infusion during CO_2 inhalation, which will produce only a meager bicarbonate diuresis, does not inhibit a mercurial effect.[12] Finally, an extracellular alkalosis as produced by potassium depletion but without an accompanying bicarbonate diuresis (because of the forced extrusion of hydrogen into the tubular fluid) will not enhance or diminish a mercurial diuresis.[48] In summary, these observations suggest that any technique whereby additional sodium is swept into the distal tubule will serve to augment mercurial diureses, provided the urine remains acid. On the other hand, the presence of bicarbonate in the distal tubular fluid, regardless of the solute supply, will tend to inhibit a mercurial diuresis. It may be relevant that the most marked changes in tubular pH develop within the late distal tubule.[54, 55]

In summary, data have been presented which in man at least contradict the plausibility of a primary proximal tubular site of action of organomercurials. It has been suggested that the major site of action may reside within the late distal tubule. While this hypothesis remains to be substantiated, the proposal does help explain many of the features of a mercurial diuresis as well as many physiological or clinical alterations that augment or inhibit a mercurial diuresis.

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